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Use of Ibutilide in Cardioversion of Patients With Atrial Fibrillation or Atrial Flutter Treated With Class IC Agents

Richard H. Hongo, MD,* Sakis Themistoclakis, MD,† Antonio Raviele, MD,† Aldo Bonso, MD,† Antonio Rossillo, MD,† Kathryn A. Glatter, MD, FACC,‡ Yanfei Yang, MD,* Melvin M. Scheinman, MD, FACC*

San Francisco and Davis, California; and Mestre-Venice, Italy

OBJECTIVES We sought to assess the efficacy and safety of ibutilide cardioversion for those with atrial fibrillation (AF) or atrial flutter (AFL) receiving long-term treatment with class IC agents.

BACKGROUND Attenuation of ibutilide-induced QT prolongation has been observed in a small number of patients pretreated with class IC agents. The clinical significance of the interaction between ibutilide and class IC agents is unknown.

METHODS Seventy-one patients with AF (n = 48) or AFL (n = 23), receiving propafenone 300 to 900 mg/day (n = 46) or flecainide 100 to 300 mg/day (n = 25), presented for ibutilide (2.0 mg) cardioversion.

RESULTS The mean durations of arrhythmia episode and arrhythmia history were 25 ± 48 days and 4.4 ± 6.4 years, respectively. Sixty-five patients (91.5%) had normal left ventricular systolic function. Twenty-three of 48 patients (47.9%; 95% confidence interval, 33.3% to 62.8%) with AF and 17 of 23 patients (73.9%; 95% confidence interval, 51.6% to 89.8%) with AFL converted with mean conversion times of 25 ± 14 min and 20 ± 12 min, respectively. There was a small increase in corrected QT interval after ibutilide (from 442 ± 61 ms to 462 ± 59 ms, p = 0.006). One patient developed non-sustained polymorphous ventricular tachycardia and responded to intravenous magnesium. Another developed sustained torsade de pointes and was treated effectively with direct-current shock and intravenous dopamine.

CONCLUSIONS Our observations suggest that the use of ibutilide in patients receiving class IC agents is as successful in restoring sinus rhythm and has a similar incidence of adverse effects as the use of ibutilide alone. (J Am Coll Cardiol 2004;44:864–8) © 2004 by the American College of Cardiology Foundation

Class IC antiarrhythmic agents are frequently used in the management of patients with atrial fibrillation (AF) or atrial flutter (AFL) and are recommended as first-line antiarrhythmic therapy of AF in patients with no or minimal heart disease (1). At times, the use of these agents in patients with AF may result in the induction of AFL, or so-called IC flutter (2). Despite the use of catheter ablation to treat AF and AFL in selected patients, recurrences of these arrhythmias and the development of IC flutter are common experiences, and the evaluation of cardioversion techniques is appropriate.

Ibutilide has been found in comparative studies to be the most effective intravenous agent for conversion of AF and AFL (3–5). In the only reported study that has specifically evaluated the interaction of ibutilide with class IC agents, Reiffel et al. (6) found that pretreatment with either propafenone or flecainide in six patients attenuated ibutilide-induced corrected QT (QT_C) interval prolongation without altering ibutilide efficacy. Ibutilide has been found to both block the delayed rectifier potassium current (7) and enhance the slow inward sodium current (I_{Na}) (8), and it is thought to exert its class III antiarrhythmic effect by one or both mechanisms. Class IC agents primarily block fast I_{Na}, may conceivably curtail the degree of prolongation in action potential duration caused by the enhancement of slow I_{Na} by ibutilide, and may consequently decrease the incidence of adverse effects and/or efficacy of ibutilide. The purpose of our study was to assess the efficacy and safety of ibutilide cardioversion for those with AF or AFL receiving long-term treatment with class IC agents.

METHODS

Patients. Seventy-one consecutive patients, receiving either propafenone or flecainide for treatment of AF or AFL, presented for elective cardioversion of either AF or AFL. Patients were recruited from two centers (University of California, San Francisco, and Umberto I Hospital, Mestre-Venice, Italy) and were evaluated prospectively. Patients were excluded if they were <18 years of age, of childbearing potential, or receiving an antiarrhythmic agent other than a class IC agent. Patients were also excluded if they had a previous episode of torsade de pointes, a QT_C interval >500 ms, a systolic blood pressure <90 mm Hg, a heart rate <60 beats/min, a left ventricular (LV) ejection fraction (EF) <40%, or evidence of active ischemic heart disease.

Ventricular rate control was permitted with beta-blocker,

From the *University of California, San Francisco, San Francisco, California; †Umberto I Hospital, Mestre-Venice, Italy; and ‡University of California, Davis, Davis, California. Dr. Scheinman is on the speaker bureau for 3M (maker of flecainide).

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Abbreviations and Acronyms

AF = atrial fibrillation
AFL = atrial flutter
CI = confidence interval
ECG = electrocardiogram/electrocardiographic
EF = ejection fraction
I_{Kr} = delayed rectifier potassium current
I_{Na} = sodium current
LV = left ventricle/ventricular
QT_C = corrected QT (interval)
SR = sinus rhythm

calcium-channel blocker, or digoxin. Left ventricular systolic function was assessed by echocardiography; LVEF ≥50% was considered normal. Anticoagulation therapy was instituted before cardioversion if the duration of arrhythmia was >48 h. When clinically indicated, a transesophageal echocardiography was performed to exclude intracardiac thrombus. The duration of arrhythmia was measured in days, from recognition of persistent arrhythmia to cardioversion. A duration <24 h was counted as one day for purposes of analysis. Serum potassium and magnesium levels were assessed before cardioversion, and electrolytes were supplemented if the potassium level was <4.0 mmol/l or the magnesium level was <1.6 mmol/l. Patients did not receive magnesium prophylactically. The institutional review board from each center approved the study, and informed consents were obtained from the participating patients.

Cardioversion protocol. Cardioversions were performed in a cardiac electrophysiology laboratory or an intensive care unit capable of continuous electrocardiographic (ECG) monitoring. External cardioverter defibrillator pads were placed in anterior-posterior configuration and were connected to a direct-current cardioverter defibrillator unit. One milligram of ibutilide (Pharmacia & Upjohn Co., Kalamazoo, Michigan) was infused intravenously through a peripheral vein over 10 min. This was followed by a 10-min observation period. If patients did not convert to sinus rhythm (SR) by the end of the observation period, an additional 1 mg was administered over 10 min. Infusion was stopped for termination of arrhythmia, development of dysrhythmia, or QT-interval prolongation >600 ms. If patients did not convert to SR after completion of the second infusion, conventional synchronized direct-current cardioversion was performed within 30 min (within 60 min of ibutilide initiation). It was recognized that while this was a relatively short post-ibutilide (to direct-current shock) period, pressures of laboratory and intensive care unit utilization made this compromise necessary. When possible, however, patients were observed a full 1 h from time of ibutilide initiation before proceeding with direct-current cardioversion. All patients were observed with continuous ECG monitoring for 4 h after ibutilide infusion.

ECG measurements. A 12-lead ECG was obtained before ibutilide infusion (during arrhythmia) and after cardioversion (during SR). Electrocardiograms were recorded at 25 mm/s paper-speed, and the QT interval was assessed in leads without U waves. The QT interval was measured from the initiation of the QRS complex to the intersection of the T-wave downslope extension and the baseline. When the QT interval during atrial arrhythmia was difficult to ascertain because of fibrillatory or flutter waves, the QT interval after conversion to SR was used to help clarify the end of the QT interval (Fig. 1). The RR interval was measured as the distance between two consecutive R-wave peaks. In patients with AF, we measured RR and QT intervals from five consecutive beats. The mean RR interval and the longest

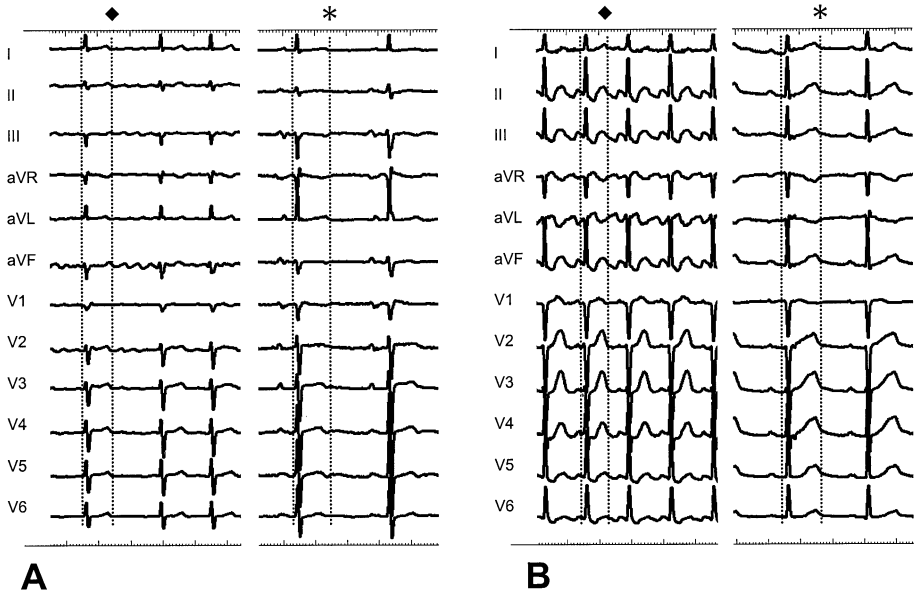

Figure 1. Assessment of QT interval during atrial arrhythmia and sinus rhythm. **(A)** The end of the QT interval **(diamond)** during atrial fibrillation is clarified by comparing it with the end of the QT interval in sinus rhythm **(*)** after conversion. **(B)** The end of the QT interval **(diamond)** during atrial flutter is clarified by comparing it with the end of the QT interval in sinus rhythm **(*)** after conversion.

QT interval were used for analysis. Two experienced cardiologists, one who was kept unaware of the study protocol (Y.Y.), independently read 20 randomly selected ECGs in order to assess the reproducibility of QT measurement. The intra- and inter-observer Pearson's correlation coefficients of the measured QT interval during atrial arrhythmia were 0.972 and 0.967, respectively. The intra- and inter-observer correlation coefficients of the measured QT interval after conversion to SR were 0.968 and 0.970, respectively. The QT_C interval was calculated using Bazett's formula.

Statistical analysis. Continuous variables were expressed as mean ± SD and were analyzed using the Student *t* test. Categorical data were analyzed using the Fisher exact test. A p value of <0.05 was considered significant. The STATA version 8.0 (StataCorp, College Station, Texas) program was used to calculate binomial 95% confidence intervals (CI) for response rates and adverse event rates. Time-to-event curves (Kaplan-Meier analysis) were constructed using ibutilide conversion data to estimate the rate of successful ibutilide conversion over time. Column charting was used to illustrate the difference in mean QT_C interval (analyzed by paired Student *t* test) before and after ibutilide.

RESULTS

Patient characteristics. A total of 71 patients (56.3% male, 64 ± 14 years old) were studied. Forty-eight patients (67.6%) presented for cardioversion of AF and 23 patients (32.4%) for AFL. The mean and median durations of the arrhythmia episode were 25 ± 48 days and 2 days, respectively (range: 1 to 240 days). The mean and median durations of arrhythmia history were 4.4 ± 6.4 years and 2 years, respectively. Sixty-five patients (91.5%) had normal LV systolic function. The LVEF of the six patients with depressed function ranged between 40% and 45%. These patients had no history or signs of either active ischemic heart disease or congestive heart failure, and they were deemed safe to receive ibutilide infusion.

Forty-six patients (64.8%) were receiving propafenone 554 ± 175 mg/day (300 to 900 mg/day), and 25 patients (35.2%) were treated with flecainide 226 ± 65 mg/day (100 to 300 mg/day). The mean and median duration of class IC agent therapy was 345 ± 481 days and 106 days, respectively. Twenty-one patients had been previously treated with another antiarrhythmic agent (quinidine [1 patient], procainamide [2 patients], sotalol [9 patients], amiodarone [8 patients], and dofetilide [1 patient]), and 4 patients had been treated separately with both a class IA agent (quinidine [1 patient], procainamide [3 patients]) and sotalol. Table 1 lists baseline characteristics by arrhythmia type.

Conversion rates. Twenty-three of 48 patients (47.9%; 95% CI, 33.3% to 62.8%) with AF converted to SR after ibutilide with a mean conversion time of 25 ± 14 min. Seventeen of 23 patients (73.9%; 95% CI, 51.6% to 89.8%) with AFL converted to SR after ibutilide with a mean conversion time of 20 ± 12 min. Of the 42 patients that did not convert after 30 min, 27 (64.3%) were observed beyond 30 min. Figure 2 shows the time-to-event curves for both patients with AF and AFL. Most conversions for both AF and AFL patients occurred within 30 min of ibutilide initiation, but conversion continued to occur beyond 30 min. All 31 patients who did not convert with ibutilide had successful and uneventful electrical cardioversions. No patient had termination of ibutilide infusion for either ventricular dysrhythmia or excessive QT prolongation.

For the study population as a whole, there was no statistical difference in the ibutilide conversion rate between

Table 1. Baseline Characteristics by Arrhythmia Type

	AF (n = 48)	AFL (n = 23)
Demographics		
Age, yrs	64 ± 16	65 ± 8
Male	19 (39.6)	15 (65.2)
Clinical data		
Arrhythmia duration*, days	32 ± 54	11 ± 27
Arrhythmia history, yrs	4.3 ± 5.3	4.6 ± 8.3
LVEF, ≥50%	44 (91.7)	21 (91.3)
Associated diagnoses		
Hypertension	13 (27.1)	10 (43.5)
COPD	1	2
Previous PE	2	0
Diabetes	0	2
CAD	1	0
Dilated CM	1	0
Hyperthyroidism	1	0
Antiarrhythmic agents		
Propafenone	32 (66.7)	14 (60.9)
Flecainide	16 (33.3)	9 (39.1)
Therapy duration†, days	346 ± 543	340 ± 304
AVN blocking agents		
Any agent‡	24 (50.0)	8 (34.8)
Beta-blocker	16 (33.3)	1 (4.3)
Calcium-channel blocker	5 (10.4)	5 (21.7)
Digoxin	4 (8.3)	3 (13.0)

*Duration of arrhythmic episode for which patient presents for cardioversion; †Duration of class IC agent therapy before cardioversion; ‡One patient in each group was receiving multiple agents. Data are presented as n (%) or mean ± SD.

AF = atrial fibrillation; AFL = atrial flutter; AVN = atrioventricular node; CAD = coronary artery disease; CM = cardiomyopathy; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; PE = pulmonary embolism.

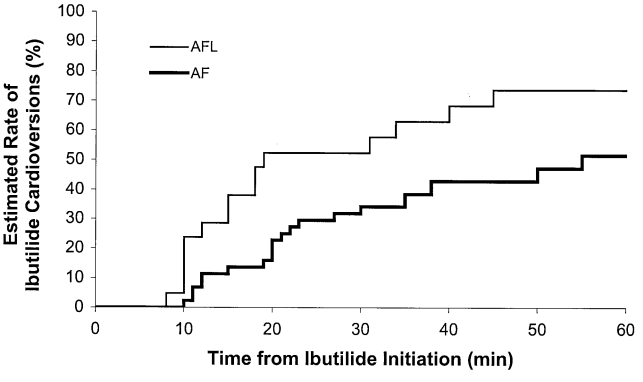

Figure 2. Time-to-event curves showing the estimated rate of ibutilide conversions during the 60-min observation period after ibutilide initiation, by arrhythmia type. AF = atrial fibrillation; AFL = atrial flutter.

Table 2. Predictors of Ibutilide Cardioversion Success by Univariate Analysis

	Conversion (n = 40)	No Conversion (n = 31)	p Value
Age, yrs	63 ± 15	66 ± 12	0.356
Male	22 (55.0)	18 (58.1)	0.494
LVEF, ≥50%	34 (85.0)	31 (100.0)	0.027*
Hypertension	13 (32.5)	10 (32.3)	0.594
Propafenone use	28 (70.0)	18 (58.1)	0.213
AVN blocker use	18 (45.0)	14 (45.2)	0.589
AFL	17 (42.5)	6 (19.4)	0.034
Arrhythmia duration, days	22 ± 46	30 ± 51	0.462
Arrhythmia duration, ≤1 day	20 (50.0)	14 (45.2)	0.435
Arrhythmia duration, ≤7 days	26 (65.0)	17 (54.8)	0.266
AF duration†, ≤1 day	11 (47.8)	8 (32.0)	0.205
AF duration†, ≤7 days	15 (65.2)	11 (44.0)	0.118
Baseline HR, beats/min	107 ± 25	99 ± 23	0.193
Baseline QTc, ms	437 ± 66	452 ± 53	0.302
QTc increase, ms	12 ± 52	33 ± 55	0.144

*More patients with normal left ventricular ejection fraction (LVEF) in nonconverters; †n = 48, patients with AF. Data are expressed as n (%) or mean ± SD.

AF = atrial fibrillation; AFL = atrial flutter; AVN = atrioventricular node; HR = heart rate; LVEF = left ventricular ejection fraction; QTc = corrected QT interval.

those with arrhythmia duration of ≤1 day (n = 33) and those with arrhythmia duration of >1 day (60.6% vs. 54.1%, p = 0.378). Likewise, there was no statistical difference in the ibutilide conversion rate between those with arrhythmia duration of ≤7 days (n = 42) and those with arrhythmia duration of >7 days (61.9% vs. 50.0%, p = 0.230). In patients with AF, however, there was a trend toward a higher ibutilide conversion rate in those with arrhythmia duration ≤7 days (n = 27) than in with those with arrhythmia duration >7 days (59.3% vs. 33.3%, p = 0.067) and, similarly, a higher conversion rate in those with arrhythmia duration ≤1 day (n = 21) than in those with duration >1 day (61.9% vs. 37.0%, p = 0.078). The only variable that clearly predicted success of ibutilide conversion by univariate analysis was presence of AFL (Table 2).

Effect of ibutilide on ECG. Overall, there was a statistically significant increase in QT interval (352 ± 55 ms to 439 ± 62 ms, p < 0.001) and QT_C interval (442 ± 61 ms to 462 ± 59 ms, p = 0.006) (Fig. 3) after ibutilide. The difference in QT_C interval before and after ibutilide was significant in patients with AF (453 ± 57 ms vs. 478 ± 60 ms, p = 0.004) but was not of statistical significance in patients with AFL (418 ± 61 ms vs. 433 ± 46 ms, p = 0.252). Overall, the mean QT_C interval change was 20 ± 54 ms.

Adverse effects of ibutilide. Two patients (2.8%; 95% CI, 0.3% to 9.8%) developed significant ventricular dysrhythmias after conversion to SR after ibutilide infusion. A 62-year-old woman had frequent episodes of non-sustained polymorphous ventricular tachycardia after electrical conversion to sinus bradycardia (50 beats/min) that was associated with QT prolongation (500 ms). The dysrhythmia was effectively suppressed with magnesium infusion. A 92-year-old woman presented with AF and rapid ventricular rate and was treated with propafenone, beta-blocker, and digoxin. She developed sustained torsade de pointes after ibutilide conversion to profound sinus bradycardia (28 beats/min) with marked QT-interval prolongation (600 ms) and was successfully treated with electrical cardioversion. She continued to have non-sustained polymorphous ventricular tachycardia after conversion despite magnesium and isoproterenol infusions, but she eventually responded to dopamine infusion. Both women had normal baseline QT intervals (360 and 320 ms, respectively), had normal LV function, and were subsequently confirmed to have sinus node dysfunction. Another patient developed a reversible complete right bundle branch block (QRS duration: 160 ms) during and for several hours after ibutilide infusion without apparent clinical consequence.

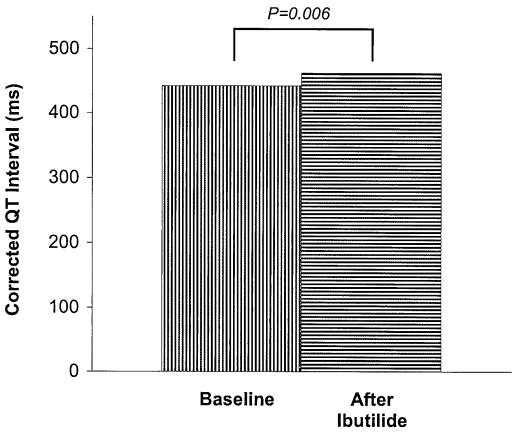

Figure 3. Change in overall corrected QT interval after ibutilide infusion.

DISCUSSION

Efficacy of combined ibutilide and class IC agent. Three large randomized placebo-controlled clinical trials (9–11) established the efficacy of ibutilide and found 90-min (from ibutilide initiation) conversion rates of 29%, 31%, and 28% for AF and 38%, 63%, and 61% for AFL. Other randomized studies (3–5) compared ibutilide with other antiarrhythmic agents and found 60- to 90-min ibutilide conversion rates of 32% to 51% for AF and 64% to 76% for AFL. In the only report that used ibutilide in combination with another antiarrhythmic agent, the 30-min conversion rate in patients receiving concomitant amiodarone therapy was observed to be 39% for AF and 54% for AFL (12).

Although direct comparisons among studies with differing design cannot be made, ibutilide conversion rates in this study appear to be in the range of most reports. Furthermore, because the observation time in our study (30 to 60 min from ibutilide initiation) was shorter than what was used in most previous reports, the conversion rates that we found may underestimate the overall efficacy of therapy. Although the majority of conversions in our study occurred within 30 min, continued conversions between 30 and 60 min (Fig. 2) suggest that there might have been higher conversion rates if all patients were observed for a full hour

(only 64.3% of patients not converted after 30 min were observed beyond 30 min).

Safety of combined ibutilide and class IC agent. In the three major randomized placebo-controlled clinical trials, the occurrences of sustained torsade de pointes were 2.4%, 1.7%, and 2.3% (9–11). A meta-analysis of five studies (586 patients) found the occurrence of sustained torsade de pointes with ibutilide to be 1.7% (13). Again, although a direct comparison cannot be made, the risk of sustained torsade de pointes in this study appears similar to that of previous reports. The single occurrence of sustained torsade de pointes in this study was in the setting of profound sinus node suppression after conversion, and it emphasizes the importance of assessing the presence of sinus node dysfunction before the use of ibutilide and avoiding overly aggressive heart rate control immediately before cardioversion.

Attenuation of ibutilide-induced QT_C prolongation. Dose-dependent mean increase in QT_C interval after ibutilide infusion has been reported in the range of 47 to 90 ms (10,11,14). Mean ibutilide-induced QT_C interval prolongation was attenuated (20 ± 54 ms), but without decrease in ibutilide efficacy, in our study. This attenuation of ibutilide-induced QT prolongation suggests that class IC agents block slow inward I_{Na} in addition to fast I_{Na}.

Study limitations. Because this study was not placebo-controlled, the efficacy beyond that of placebo is not known. The observed safety of ibutilide use in this study may have been influenced by the nature of the study population. Because class IC agents are not used in patients with significant structural heart disease, the study inherently selected patients with a lower risk of proarrhythmia. In addition, 25 patients had been previously treated with either a class IA and/or class III antiarrhythmic agent without developing sustained torsade de pointes, perhaps suggesting a lower susceptibility to proarrhythmia in these patients. Insufficient power may explain the inability to find variables other than arrhythmia type that predicted conversion success.

Reprint requests and correspondence: Dr. Melvin M. Scheinman, Section of Cardiac Electrophysiology, University of California, San Francisco, 500 Parnassus Avenue, MU-East 4S, Box 1354, San Francisco, California 94143-1354. E-mail: scheinman@medicine.ucsf.edu.

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